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Enantiomorphic symmetry breaking in crystallization of molten sodium chlorate**

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Abstract

Enantiomorphic symmetry breaking of stirred samples of sodium chlorate is demonstrated, revealing the unexpected involvement of an achiral solid phase. The results should stimulate future computational models of nucleation, including symmetry breaking, and have implications for mechanisms that invoke enantiomorphism in natural minerals to explain biohomochirality.

Introduction

Chirality, or mirror symmetry, is arguably one of the most important classes of symmetry which pervades the natural sciences, chemistry in particular. One key challenge to chemists is asymmetric synthesis: discovering the means to create chiral substances. Another key challenge is to understand biohomochirality: the remarkable conclusion that life evolved into favouring one side of the molecular mirror, e.g., the observed prevalence of l-amino acids in life.

In addition to molecular chirality, solid crystals can form in one of 65 different chiral space groups. This can happen even when the molecules are not themselves chiral, but co-operate to form a macroscopic arrangement that is chiral: the left and right handed forms of the solid are known as enantiomorphs. Optical activity of the solid allows us to assign levorotatory (*l*) and dextrorotatory (*d*) enantiomorphs. Prime examples of chiral solids are the abundant natural mineral α-quartz (SiO_2, space group $P3_121$ for *l*-α-quartz), and sodium chlorate ($NaClO_3$, space group $P2_13$). A preference for adsorption of one enantiomer of a racemic mixture of molecules onto the surface of an enantiomorphic mineral has been suggested as a viable starting point for reaction pathways leading to homochirality.[1] It appears, however, that this would require a net abundance of one enantiomorph: if not globally, at least in local regions on the earth: how, or if, this happens remains a question for debate.[2] The link between asymmetric crystallization and asymmetric synthesis has been neatly demonstrated by the experiments of Soai et al.,[3] who have shown that crystals of *d*-α-quartz and *d*-$NaClO_3$ can bias the autocatalytic synthesis of (*S*)-5-pyramidyl alkanols up to 98% enantiomeric excess: likewise it was found that *l*-α-quartz or *l*-$NaClO_3$ favours synthesis of the (*R*) enantiomer.[4, 5]

Spontaneous resolution of chiral molecules is possible when the rate of crystallization is competitive with the interconversion between enantiomers.[6, 7] For achiral compounds, enantiomorphic resolution can be achieved by mechanical means. If a static, aqueous solution of $NaClO_3$ is left to evaporate, statistically equal numbers of *l* and *d* crystals are formed.[8] Kondepudi et al., however, showed that stirring of the solution cab produce crystals of a single enantiomorph, i.e., enantiomorphic symmetry breaking.[9] By the time the solution has evaporated to become supersaturated, all that is required is the formation of a single nucleus of one enantiomorph, known as primary nucleation. This single nucleus

ripens to become a viable seed, which can then produce numerous secondary nuclei of the same enantiomorph. These secondary nuclei are cycled through the metastable liquid by the stirring, causing further nucleation of the same enantiomorph. The mechanism for rapid secondary nucleation is analogous to autocatalysis, and is promoted by both hydrodynamic shear and by collisions of the nuclei in the solution.[10] The chiral outcome (*d* or *l*) in a single stirred vessel was statistical because the primary nucleation process is not biased by the stirring.[9]

External influences, such as exposure to β radiation, have been shown to bias the crystallization of sodium chlorate,[11] although doubt has been cast recently over the influence of chiral co-solutes such as d-glucose.[12] In recent work, Viedma has shown that grinding of solid sodium chlorate in contact with its saturated solution will transform to favour one enantiomorph over the other after some hours.[13] Osuna–Esteban has demonstated a similar asymmetric growth of crystals by mechanical methods using an aerosol–liquid cycle,[14] which recycles small crystallites through the solution phase and eventually causes complete symmetry breaking to favour one enantiomorph. Cuccia has also demonstrated symmetry breaking of ethylenediamine sulphate crystals by grinding; the chiral outcome was biased by presence of small concentrations (~10^{-1} M) of amino acids.[15, 16]

The mechanism for secondary nucleation from a primary nucleus or parent crystal is still poorly understood. At the present time, the involvement of a liquid solvent makes it very challenging to model the dynamics of secondary nucleation by computational methods. In this communication, we present the first report of enantiomorphic symmetry breaking in crystallization from a stirred, molten inorganic salt: sodium chlorate. In addition to crystallization to *l* and *d* forms of cubic $NaClO_3$, the results surprisingly implicate formation of an additional, achiral solid polymorph as an intermediate during supercooling.

Briefly, the experiments were carried out as follows. Approximately 2.5 g of sodium chlorate (99+%, Sigma–Aldrich) was added to a pyrex test tube (diameter 12 mm) along with an 8 × 2 mm polytetrafluoroethylene (PTFE) stirring bar. The tube was placed inside a brass heating block, which was seated on a magnetic hotplate with temperature controller (Heidolph MR2002). The sodium chlorate was heated to 280 °C and held at this temperature for 20 minutes to melt completely, while stirring at 750 revolutions per minute (rpm). Various stirring speeds between 250 and 1250 rpm were tested, and 750 rpm was chosen to cause smooth and rapid mixing without splashing. The temperature was reduced in stages by ~1 °C every minute until nucleation of the melt. Solidification occured instantaneously, resulting in a fused solid polycrystalline mass. Since the solid was translucent white, it was not possible to determine overall chirality by measuring optical rotation *in situ*. After cooling to room temperature, the form of the resulting solid was tested by grinding the cooled solid, which was used to seed an aqueous supersaturated (105%) solution of sodium chlorate. The chiralities of the resulting crystals were determined by measuring the direction of optical rotation of polarized white

light.[12] Samples were categorized as one of the following: seeded crystals were found to be pure dextrorotatory (*d*), pure levorotatory (*l*), or a mixture (*dl*). This seeding procedure was verified with mixtures of crystalline samples of known chirality. For the samples listed as mixed (*dl*), we did not attempt to estimate an enantiomorphic excess, because the result would be biased by the seeding procedure.

The melting point of sodium chlorate is widely quoted as 248 °C.[17] Table 1 shows the outcome obtained from cooling molten samples to the melting point of 248 °C and holding them close to this temperature (typically within ± 2 °C) until nucleation occurred. It was found that approximately equal numbers of *d*, *l* and *dl* samples were produced. Given the enforced holding temperature, all samples were found to nucleate at around the same temperature.

Enantiomorph	*d*	*l*	*dl*	total
Number of samples	9	9	8	26
Mean nucleation temperature / °C	248 ± 1	247 ± 1	246 ± 1	247 ± 1

Table 1. Results from crystallization of molten $NaClO_3$ with stirring at 750 rpm, obtained by cooling and maintaining the samples close to 248 °C. Samples labelled *d* or *l* were observed to be pure enantiomorphs, whereas *dl* represents a mixed sample.

To determine if supercooling caused a significant change in the outcome, we allowed samples of the melt to cool below 248 °C while maintaining stirring at 750 rpm. The results are shown in Table 2, where it can be seen that again, approximately equal numbers of *d*, *l* and *dl* samples were obtained.

Enantiomorph	*d*	*l*	*dl*	total
Number of samples	8	6	5	19
Mean nucleation temperature / °C	242 ± 2	245 ± 2	240 ± 1	242 ± 3

Table 2. Results from crystallization of stirred molten $NaClO_3$, allowing a total of 19 samples to supercool below the nominal melting point of 248 °C.

In Tables 1 and 2, we see that roughly two thirds of all samples show enantiomorphic symmetry breaking to *d* or *l* forms. We would expect the mechanism for symmetry breaking in the stirred molten samples to be analogous to that observed in aqueous solution.[9] Primary nucleation of an enantiomorph occurs randomly and the nucleus ripens to become a seed that creates multiple secondary nuclei of the same enantiomorph, which are distributed throughout the sample by the rapid stirring. The question arises then: what is the mechanism for producing the *dl* samples that we observe?

If the rate of stirring were too slow, we would expect to see incomplete symmetry breaking. This could occur when at least one nuclei of each symmetry is formed in a short time interval; these nuclei may each ripen to produce secondary nuclei such that neither *d* or *l* enantiomorph dominates the final solid. For stirred aqueous solutions, Kondepudi et al. observed that the enantiomorphic excess at high stirring rates (> 600 rpm) was essentially unity.[18] Compared to previous work, the ratio of the volume of our stir bar to that of the sample was much larger (×3.6), as was the length of the bar compared to the diameter of the sample (×2.1), meaning that the rate of mixing should be much greater.

To calculate the probability of obtaining a mixed *dl* sample by multiple nucleation, we developed a model based on a Poisson arrival process (see ESI for details†). The model gives the conditional probability of obtaining a pure ($P_{\mathrm{d\ or\ l}}$) or a mixed (P_{dl}) sample, given that nucleation occurs, as a function of the Poisson rate, λ. The model probabilities are shown in Fig. 1. From the fraction of mixed samples observed in the experiments ($P_{\mathrm{dl}} \approx 0.333$, Table 1), our model predicts $\lambda_{\mathrm{model}} = 1.386$ s^{-1}. On the other hand, the experimental Poisson rate, $\lambda_{\mathrm{exp}} = 0.011 \pm 0.001$ s^{-1} was estimated by fitting the times taken to nucleate for the 26 samples held at fixed temperature, defining $t = 0$ s at the moment the sample reaches 248 °C. We conclude that the experimental rate is significantly lower than would be needed for multiple nucleation to explain the observed fraction of mixed *dl* samples.

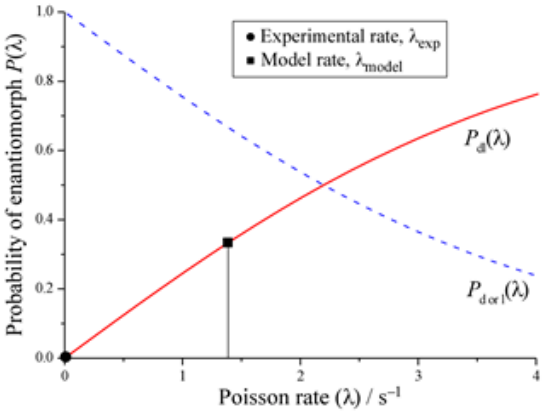

Fig. 1. Plot of the Poisson nucleation model showing probabilities of obtaining samples of pure enantiomorphs (dashed line, $P_{\mathrm{d\ or\ l}}$), or mixed samples (solid line, P_{dl}) as a function of the Poisson rate (λ). Also shown are the experimental rate obtained from analysis of nucleation times (circle, near origin), compared to the expected model rate based on the fraction (~1/3) of *dl* samples listed in Table 1 (square).

A plausible alternative explanation for the observation of the mixed *dl* samples, is the formation of other polymorphs of sodium chlorate. Meyer et al. carried out a detailed study of $NaClO_3$ in the range 230–262 °C, reporting three solid phases and various transformations between them.[19] Phase I is the common enantiomorphic cubic phase ($P2_13$) obtained at ambient temperature by crystallization from solution. Phase III is an achiral monoclinic phase ($P2_1/a$). The structure of phase II remains undetermined, but is distinguishable on account of its lack of birefringence. Below 230 °C, it was observed that all of the phases transform spontaneously to the cubic phase I. The phase III→I transition was found to be particularly facile since it is due to a simple, co-ordinated sliding of crystal layers.[20]

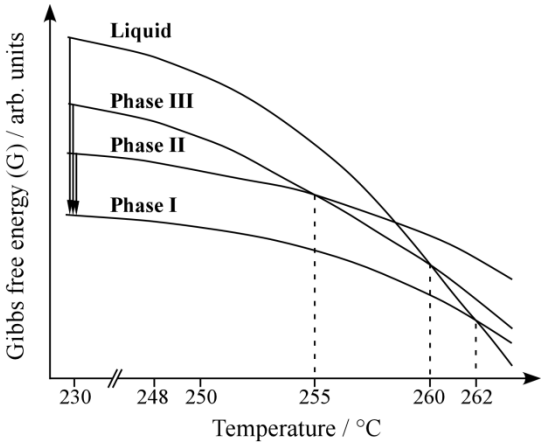

Fig. 2. Schematic phase diagram showing Gibbs free energy as a function of temperature, including solid and liquid phases of $NaClO_3$. Adapted from Meyer *et al*.[19]

The work of Meyer *et al*. indicates that the free energies of all the phases are very similar in the temperature range of our experiments (around 248 °C). Our observation of mixed *dl* samples may be explained by formation of a single nucleus of an achiral phase (II or III), which ripens to produce many secondary achiral nuclei that are circulated rapidly in the remainder of the metastable liquid eventually forming an achiral solid sample. As the solid is cooled below 230 °C, the achiral phase will transform spontaneously to a random mixture of *d* and *l* forms over a range of crystallite domains in the fused sample. Primary nucleation of the achiral phase would be competitive with nucleation of phase I in either *d* or *l* form, explaining the nearly equal numbers of *d*, *l* and *dl* samples, as we observe.

To summarize, we have demonstrated enantiomorphic symmetry breaking resulting from rapid stirring during cooling of a molten inorganic salt ($NaClO_3$). Unlike previous studies in aqueous environments, we observe formation of mixed enantiomorph (*dl*) samples. The results implicate nucleation of an achiral phase near the melting point, which undergoes a solid-to-solid transition to

give the solid cubic chiral phase consisting of random domains of *l*- and *d*-$NaClO_3$. We conclude by noting the following: (1) the present work more easily lends itself to detailed computational modelling of the dynamics of nucleation,[21] including the symmetry breaking; and, (2) by analogy we illustrate a potential mechanism for production of local regions of enantiomorphically enriched minerals from mechanically agitated melts, as would be required for explanations of biohomochirality that implicate enantioselective adsorption and reaction on these minerals, e.g., on α-quartz.[1, 2]

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